

MODERNA/NIH WIPO 2020/160397, LNP

WO 2020/160397 PCT/US2020/016082

METHODS OF PREPARING LIPID NANOPARTICLES

Related Application

[0001] This application claims priority to, and the benefit of, U.S. Provisional Application No. 62/799,620, filed January 31, 2019, the entire contents of which is incorporated herein by reference.

Field of Disclosure

[0002] The present disclosure provides novel methods of producing nucleic acid lipid
nanoparticle (LNP) formulations, the produced formulations thereof, and the related
therapeutic and/or diagnostic uses, such as methods involving the nucleic acid lipid
nanoparticles to deliver one or more therapeutics and/or prophylactics, such as a nucleic acid,
to and/or produce polypeptides in mammalian cells or organs.

Background

[0003] The effective targeted delivery of biologically active substances such as small molecule drugs, proteins, and nucleic acids represents a continuing medical challenge. In particular, the delivery of nucleic acids to cells is made difficult by the relative instability and low cell permeability of such species. Thus, there exists a need to develop methods and compositions to facilitate the delivery of therapeutics and prophylactics such as nucleic acids to cells.

[0004] Lipid-containing nanoparticles or lipid nanoparticles, liposomes, and lipoplexes have proven effective as transport vehicles into cells and/or intracellular compartments for biologically active substances such as small molecule drugs, proteins, and nucleic acids. Though a variety of such lipid-containing nanoparticles have been demonstrated, improvements in safety, efficacy, and specificity are still lacking.

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31 January 2019 (31.01.2019) US

- (71) Applicant: MODERNATX, INC. [US/US]; 200 Technology Square, Cambridge, Massachusetts 02139 (US).
- (72) Inventors: SMITH, Mike; e/o ModemaTX, Inc., 200 Technology Square, Cambridge, Massachusetts 02139 (US). HORHOTA, Allen; e/o ModemaTX, Inc., 200 Technology Square, Cambridge, Massachusetts 02139 (US). AUER, Jason; e/o ModemaTX, Inc., 200 Technology Square, Cambridge, Massachusetts 02139 (US). SKINNNER, Brie; e/o ModemaTX, Inc., 200 Technology Square, Cambridge, Massachusetts 02139 (US).
- (74) Agent: ERLACHER, Heldi A. et al.; Cooley LLP, 1299 Pennsylvania Avenue, NW, Suite 700, Washington, District of Columbia 20004 (US).
- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, DI, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KK, KK, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, FG, PH, FI, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.
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Declarations under Rule 4.17:

 as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(H))

Published

- with international search report (Art. 21(3))
- with sequence listing part of description (Rule 52(a))

(54) Title: METHODS OF PREPARING LIPID NANOPARTICLES

(57) Abstract: The present disclosure provides methods of producing lipid nanoparticle (LNP) formulations and the produced LNP formulations thereof. The present disclosure also provides therapeutic and diagnostic uses related to the produced LNP formulations.

Without these lipid shells, there would be no mRNA vaccines for COVID-19



The most effective nanoparticles were ones that the body mistook as lowdensity lipoprotein (LDL) cholesterol-commonly called bad cholesterol. Proteins that recognize LDL cholesterol in the blood bound to some of Alnylam's nanoparticles and carried them to LDL receptors on liver cells, which then caused the cells to engulf the nanoparticles in an endosome. It was the kind of complex interplay that studies in a petri dish missed.

"A lot of work has gone into studying what happens inside a cell, but trying to understand the transport that occurs before these nanoparticles reach their cells is another question entirely," says Kathryn Whitehead, a nanoparticle scientist at Carnegie Mellon University. As a consequence, "we don't even screen in vitro anymore," she says. "I find it more informative to test directly in an animal."

The work was grueling, and lipids that made great nanoparticles in a petri dish would often flop in animal studies. "You can have 50 different ionizable lipids that all deliver effectively to cells in culture, and 49 of them won't work a damn in vivo," recalls Thomas Madden, who worked at Inex and is now CEO of Acuitas Therapeutics.

Ionizable lipid 4 lipids Phospholipid in LNPS Cholesterol Nucleic acid (siRNA shown) A lipid nanoparticle (LNP) contains hundreds of small interfering RNA (siRNA) molecules, each surrounded by ionizable lipids, phospholipids, and cholesterol. The outside of the particle is coated in pegylated lipids. LNPs for messenger RNA with similar ingredients but contain only a few mRNA strands.



Carnegie Mellon University

Dr. Kathryn A. Whitehead

Associate Professor, Chemical Engineering and Biomedical Engineering

The PEGylated lipids contain graphene oxide. PEGylated LNPs are made by SINOPEG in China

ge of a natural process called receptor-mediated endocytosis to get into cells, Upon binding to a cell, the nanoparticle becomes encapsulated in an even bigger ganelle called an endosome. The endosome's acidic interior protonates the heads

ids, making them positively charged. That positive charge triggers a change in the

Pegylated lipid

shape of the nanoparticle, which scientists think helps it break free from the endosome and ultimately release its RNA cargo into the cell's cytoplasm. Once released, the RNA is free to do its job.

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What's in Pfizer BNT162b and COVID-19 Injections?

PFE EUA #27034, Nov 20, 2020, pg. 11 Sec. 3. Pfizer/BioNtech COVID019 Vaccine (BNT162b) 3.1 Vaccine Composition, Dosign Regimen

The vaccine contains a nucleoside-modified messenger RNA (modRNA) encoding the viral spike glycoprotein (S) of SARS-CoV-2. The vaccine also includes the following ingredients lipids ((4-hydroxybutyl)azanediyl) bis (hexane-6,1-diyl)bis(2-hexyldecanoate), 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 1,2-distearoyl-sn- glycero-3-phosphocholine, and cholesterol), potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dihydrate, and sucrose.

Two (2) PEGylated Lipids in Pfizer BNT162b2 ALC-0135 | ALC-0159

Emergency Use Authorization (EUA) for an Unapproved Product Review Memorandum

Identifying Information

Application Type	EUA (Event-driven EUA request)		
Application Number	27034		
Sponsor	Pfizer, Inc., on behalf of Pfizer and BioNTech		
Submission Date	November 20, 2020		
Receipt Date	November 20, 2020		
Signatory Authority	Marion F. Gruber, Ph.D., Director, CBER/OVRR		
Review Team	Ramachandra Naik, Ph.D., Chair, OVRR/DVRPA; CAPT Michael Smith, Ph.D., Regulatory Project Manager, OVRR/DVRPA;		
	Susan Wollersheim, M.D., Clinical reviewer, OVRR/DVRPA; Nabil Al-Humadi, Ph.D., Toxicology reviewer, OVRR/DVRPA; Lei Huang, Ph.D., Biostatistics reviewer, OBE/DB; Haruhiko Murata, Ph.D., CMC/Product reviewer, OVRR/DVP; Xiao Wang, Ph.D., CMC/Product reviewer, OVRR/DVP; Laura Fontan, Ph.D., CMC/Facility reviewer; OCBQ/DMPQ; Kathleen Jones, Ph.D., CMC/Facility reviewer, OCBQ/DMPQ; Kerry Welsh, M.D., Pharmacovigilance reviewer, OBE/DE; Narayan Nair, M.D., Pharmacovigilance reviewer, OBE/DE; Brenda Baldwin, Ph.D., Data Integrity reviewer, OVRR/DVRPA; Bhanumathi Kannan, Ph.D., BIMO reviewer, OCBQ/DIS/BMB; Oluchi Elekwachi, Ph.D., Labeling reviewer, OCBQ/DCM/APLB		
Review Completion Date	December 11, 2020		
Established Name/Other names used during development	Pfizer-BioNTech COVID-19 Vaccine/ BNT 162b2		
Dosage Forms/Strengths and	A 0.3 mL Suspension for intramuscular injection		
Route of Administration			
Intended Use for EUA	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)		

Pfizer/BioNtech BNT162b PEGs: ALC-0315 and ALC-0159





Medicines & Healthcare products Regulatory Agency



Public Assessment Report

Authorisation for Temporary Supply

COVID-19 mRNA Vaccine BNT162b2 (BNT162b2 RNA)

concentrate for solution for injection

Department of Health and Social Care (DHSC)
Pfizer Limited & BioNTech Manufacturing
GmbH

PAR COVID-19 mRNA vaccine BNT162

A condition of authorisation under this regulation is that the manufacturer will provide further data on the drug product manufacturing process as it is scaled up.

Excipients

The excipients sucrose, sodium chloride, potassium chloride, dibasic sodium phosphate dihydrate, monobasic potassium phosphate and water for injection are all of Ph. Eur. grades, which are acceptable.

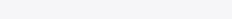
In addition to those excipients, the vaccine contains four lipids, of which two are used in approved medicinal products (cholesterol and 1,2-distearoyl-sn-glycero-3-phosphocholine, hereafter termed DSPC) and two are considered novel in that they have not been used in an authorised medicinal product in the UK:

ALC-0315 ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)) and ALC-0159 (2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide).

The lipids are intended to encapsulate the mRNA in the form of a lipid nanoparticle to aid cell entry and stability of the RNA/lipid nanoparticles.

ALC-0315 is the functional cationic lipid component of the drug product. When incorporated in lipid nanoparticles, it helps regulate the endosomal release of the RNA. During drug product manufacturing, introduction of an aqueous RNA solution to an ethanolic lipid mixture containing ALC-0315 at a specific pH leads to an electrostatic interaction between the negatively charged RNA backbone and the positively charged cationic lipid. This electrostatic interaction leads to encapsulation of RNA drug substance resulting with particle formation. Once the lipid nanoparticle is taken up by the cell, the low pH of the endosome renders the LNP fusogenic and allows the release of the RNA into the cytosol.

The primary function of the PEGylated lipid ALC-0159 is to form a protective hydrophilic layer that sterically stabilises the LNP which contributes to storage stability and reduces non-specific binding to proteins. As higher PEG content can reduce cellular uptake and interaction with the endosomal membrane. PEG content is controlled.





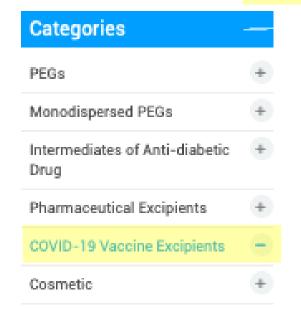


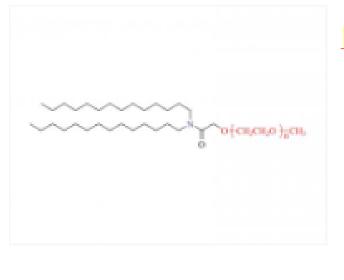
SINOPEG

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Products COVID-19 Vaccine Excipients 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide[ALC-0159] CAS: 1849616-42-7

2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 1,2-distearoyl-sn-glycero-3-phosphocholine, and cholesterol)





2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide[ALC-01591 CAS: 1849616-42-7 ALC-0159 Alternate Name: Methoxypoly(ethylene glycol) ditetradecylacetamide Abbrevition: ALC-0159, mPEG-DTA CAS: 1849616-42-7 Package Size: 1g/bottle, 10g/bottle, 100g/bottle Storage: Store at -20±5°C, keep dry research use only

Item No.: ALC-0159

Inquiry Now

Contact Us

XIAMEN SINOPEG BIOTECH CO., LTD.

Manufacturing Site: Jianye Building D, Torch Hi-Tech Industrial Development Zone, Xiang'an District, Xiamen, Fujian, China

Sales Office: 19F, ITG Business Center, No. 669 Sishui Road, Huli District, Xiamen, Fujian, China

US Tel: 1-844-782-5734 US Tel: 1-844-QUAL-PEG

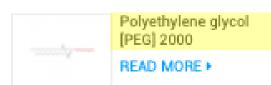
CHN Tel: 400-918-9898

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Email: sales@sinopeg.com



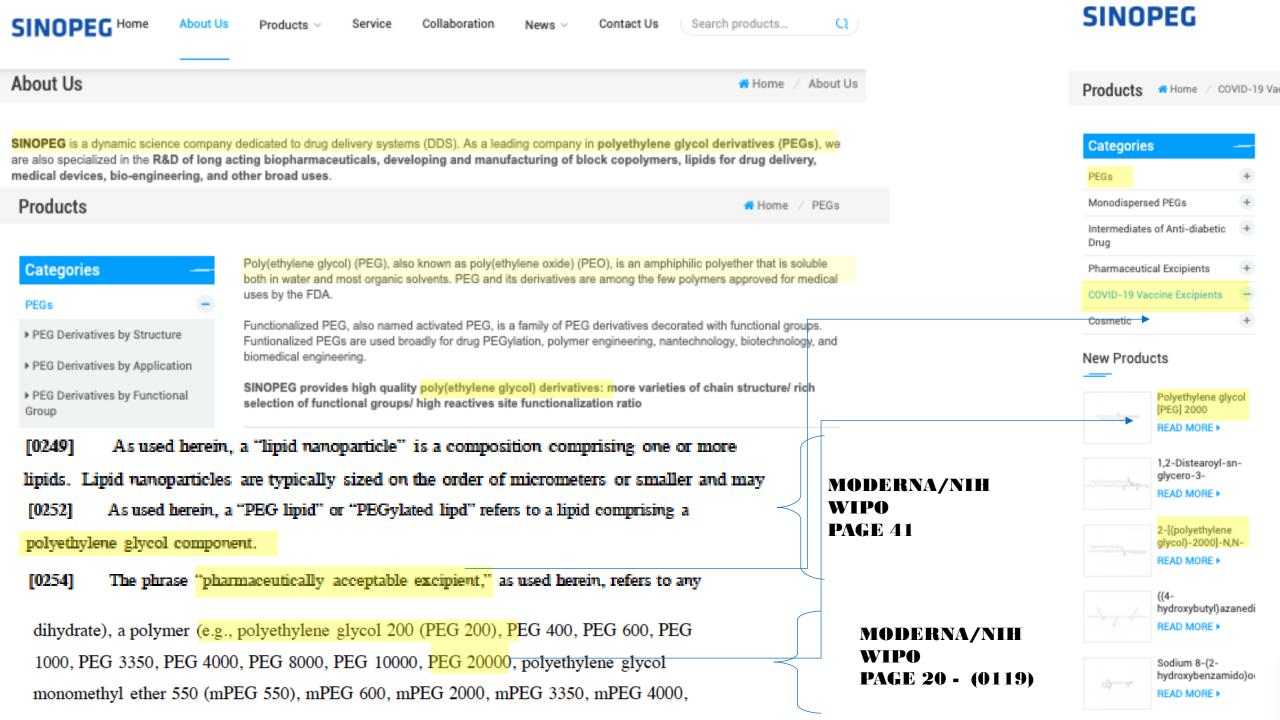
New Products



Product Details

Methoxypoly(ethylene glycol) ditetradecylacetamide

CIMODEO in coming pharmacoutical and medical devices companies around the alaba with product processes in



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Core-shell structured polyethylene glycol functionalized graphene for energy-storage polymer dielectrics: Combined mechanical and dielectric performances

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SEPTEMBER 1,2020.

Graphene, as the thinnest, strongest and stiffest material and arranged in a honeycomb pattern structure with sp2-hybridized carbon, finds more potential applications in modern industry than other carbonaceous allotropes; in pristine form, it is also an excellent heat and electric conductor. However, the major obstacle in utilizing graphene, particularly for electronic applications, is its insolubility in the fully reduced state due to the strong affinity between the graphene sheets.

In the present study, they synthesized for the first time a polydispersed graphene with desirable electric conductivity by covalent functionalization with single terminal aminated polyethylene glycol monomethyl ether (PEG-NH2). The PEG-NH2 grafted graphene (PEG@GO) was then reduced by hydrazine hydrate to PEG@rGO and subsequently incorporated into epoxy resin by a solution mixing method. The PEG@rGO with a "core-shell" structure exhibited homogeneous dispersion in epoxy and also effectively reduced the dielectric loss, hence contributing excellent dielectric properties and mechanical strength to the final PEG@rGO/epoxy nanocomposites.

Global Patent for 2019-nCov Vaccines' Graphene Lipid Nanotechnology

Nano coronavirus recombinant vaccine taking graphene oxide as Description

Abstract

The invention belongs to the field of nano materials and biomedicine, and relates to a vaccine, in particular to development of 2019-nCoV coronavirus nuclear recombinant nano vaccine. The invention also comprises a preparation method of the vaccine and application of the vaccine in animal experiments. The new corona vaccine contains graphene oxide, carnosine, CpG and new corona virus RBD; binding carnosine, CpG and neocoronavirus RBD on the backbone of graphene oxide; the CpG coding sequence is shown as SEQ ID NO 1; the novel coronavirus RBD refers to a novel coronavirus protein receptor binding region which can generate a high-titer specific antibody aiming at the RBD in a mouse body, and provides a strong support for prevention and treatment of the novel coronavirus.



Nano coronavirus recombinant vaccine taking graphene oxide as carrier

Technical Field

The invention belongs to the field of nano materials and biomedicine, and relates to development of a vaccine development platform. In particular to the development of 2019-nCoV coronavirus nuclear recombinant nano-vaccine. The invention also includes the use of the vaccine in animal testing.

Technical Field

The vaccine is an ultimate weapon for eliminating major infectious diseases, has the advantages of lowest cost and more advantages of prior enemy than other therapies, undoubtedly becomes hopeful to the public, the smallpox is eliminated by human beings through vaccination, the poliomyelitis cases are reduced by 99 percent, the infectious diseases such as diphtheria are rare, and the incidence rate of diseases such as measles, neonatal tetanus and the like is remarkably reduced. The effect of vaccines on human health is not excessive, and the birth of each new vaccine is a great victory for human beings to overcome an infectious disease! To date, no medical treatment has been able to have such an important, lasting and profound effect on human health as a vaccine; nor is any therapeutic available to eliminate a disease from the earth at the very least cost of a vaccine.

U.S. & Global Pharma & Biotech leaders meeting at Shanghai National Engineering Research Center for Nantotech to Collaborate on Global COVID-19 Vaccines

Photo directly from Shanghai National Eng Research Website

CN112220919A





Other languages: Chinese

Inventor: 崔大祥, 高昂, 梁辉, 田静, 李雪玲, 沈琦

Current Assignee: Shanghai National Engineering Research

Center for Nanotechnology Co Ltd

Worldwide applications

Application CN202011031367.1A events 3

2020-09-27 · Application filed by Shanghai National Engineering Research Center for

Nanotechnology Co Ltd

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Contact Us

XIAMEN SINOPEG BIOTECH CO., LTD.

Manufacturing Site: Jianye Building D, Torch Hi-Tech Industrial Development Zone, Xiang'an District, Xiamen, Fujian, China

Sales Office: 19F, ITG Business Center, No. 669 Sishui Road, Huli District, Xiamen, Fujian, China

US Tel: 1-844-782-5734 US Tel: 1-844-QUAL-PEG CHN Tel: 400-918-9898

QQ: 1901848004

Email: sales@sinopeg.com



PFE cGMP Procedures and Inspections is Redacted, pgs. 47-48

5.4. Chemistry, Manufacturing, and Control (CMC) Information

The manufacturing process for the BNT162b2 drug substance (DS) consists of two major steps:

(b) (4)

. The BNT162b2 drug product (DP) is manufactured by mixing the modRNA DS with lipids during lipid particle (LNP) formulation followed by fill/finish. To support the EUA request, in-process, release, and characterization data for a minimum of three process performance qualification (PPQ) DS batches for each DS manufacturing facility were provided. Certificates of Analysis (CoAs) for a minimum of three GMP commercial-scale DP lots from each DP manufacturing node were requested from the Sponsor to demonstrate DP process performance and consistency. DP data from four manufacturing nodes were available during the EUA review. In addition, to support vaccine supply and availability, data from two additional nodes will be submitted to the EUA between December 17 and December 23, 2020. Once authorized, the Sponsor will submit the CoAs of DP lots to be distributed under EUA for review at least 48 hours prior to lot distribution.

The DS manufacturing process underwent changes during vaccine development. (b) (4)

A comprehensive analytical comparability assessment has been performed and the submitted data support the comparability of (b) (4) with (b) (4) for the manufacture of BNT162b2 DS. (b) (4)

For DP, the manufacturing process was changed from a Classical process to an Upscale process involving an increase in batch size (capable of

The manufacture of the Pfizer-BioNTech COVID-19 Vaccine is performed at a number of facilities. For each of these facilities, FDA requested and reviewed information on equipment, facilities, quality systems and controls, container closure systems as well as other information as per the guidance, "Emergency Use Authorization for Vaccines to Prevent COVID-19, Octobe 2020", to ensure that there is adequate control of the manufacturing processes and facilities.

Emergency Use Authorization (EUA) for an Unapproved Product Review Memorandum

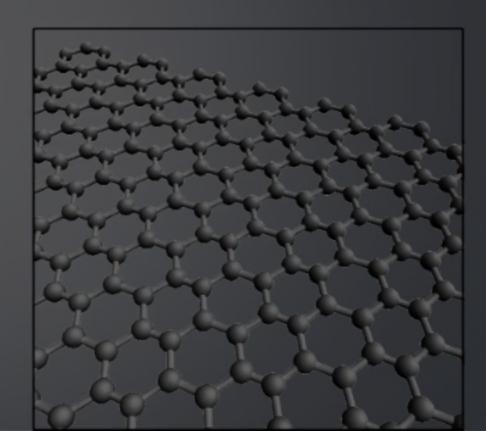
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identifying intormudent			
Application Type	EUA (Event-driven EUA request)		
Application Number	27034		
Sponsor	Pfizer, Inc., on behalf of Pfizer and BioNTech		
Submission Date	November 20, 2020		
Receipt Date	November 20, 2020		
Signatory Authority	Marion F. Gruber, Ph.D., Director, CBER/OVRR		
Review Team	Ramachandra Naik, Ph.D., Chair, OVRR/DVRPA; CAPT Michael Smith, Ph.D., Regulatory Project Manager, OVRR/DVRPA; Susan Wollersheim, M.D., Clinical reviewer, OVRR/DVRPA; Nabil Al-Humadi, Ph.D., Toxicology reviewer, OVRR/DVRPA;		
	Lei Huang, Ph.D., Biostatistics reviewer, OBE/DB; Haruhiko Murata, Ph.D., CMC/Product reviewer, OVRR/DVP; Xiao Wang, Ph.D., CMC/Product reviewer, OVRR/DVP; Laura Fontan, Ph.D., CMC/Facility reviewer; OCBQ/DMPQ; Kathleen Jones, Ph.D., CMC/Facility reviewer, OCBQ/DMPQ; Kerry Welsh, M.D., Pharmacovigilance reviewer, OBE/DE; Narayan Nair, M.D., Pharmacovigilance reviewer, OBE/DE; Brenda Baldwin, Ph.D., Data Integrity reviewer, OVRR/DVRPA; Bhanumathi Kannan, Ph.D., BIMO reviewer, OCBQ/DIS/BMB; Oluchi Elekwachi, Ph.D., Labeling reviewer, OCBQ/DCM/APLB		
Review Completion Date	December 11, 2020		
Established Name/Other names used during development	Pfizer-BioNTech COVID-19 Vaccine/ BNT162b2		
Dosage Forms/Strengths and	A 0.3 mL Suspension for intramuscular injection		
Route of Administration			
Intended Use for EUA	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)		
Intended Population	Individuals 16 years of age and older		

Why Choose Graphene Oxide as the Delivery System (excipient)?

GRAPHITE

GRAPHENE



How Small are the PEGylated Lipid

Polymer Journal

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Mil '

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Measurement Units

 $1mm = 1,000 \mu m (micrometer)$

 $1 \mu m = 1,000 nm (nanometers)$

Biological Examples:

Macrophage (WBC) = 21 μ m = 21,000 nm Red Blood Cell (RBC) = 6-8 μ m = 6,000 - 8,000 nm

Platelet 2-4 µm = 2,000 - 4,000 nm mRNA and RNA = 100's nm mRNA COV- Spike Protein = .35 nm

SARS-CoV-2 Respiratory Particles 1 4.7 μ m = 4,700 nm

PEGylated Lipid Nanoparticles2 = 10's to 100's nm

The PEGylated LNP encapsulated mRNA is 40 nm 150 nm inside the 'vaccines.' Scientists have reduced the size of SARS-CoV-2 by up to 99.15% while improving the mRNA's transmissibility, including its ability to withstands@xtremelyichars412412414111

nature > polymer journal > review > article

Review | Published: 08 May 2020

Graphene oxide-incorporated hydrogels for biomedical applications

Publish with us >

Jongdarm Yi, Goeun Choe, Junggeon Park & Jae Young Lee □

Journal information >

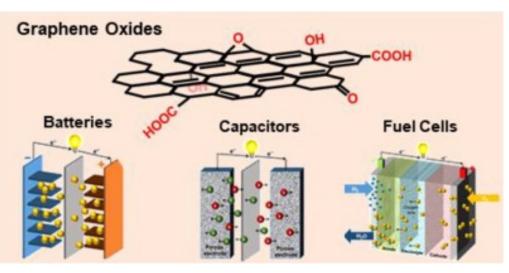
Polymer Journal 52, 823-837 (2020) | Cite this article

1362 Accesses | 14 Citations | 31 Altmetric | Metrics

Abstract

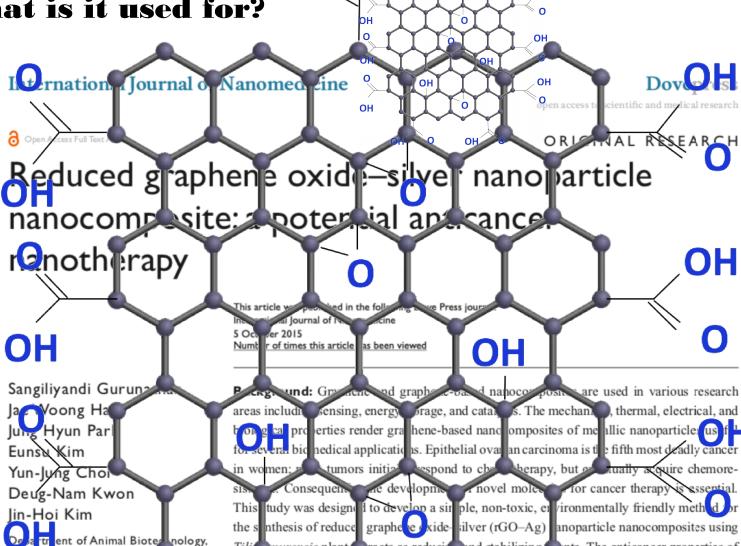
Graphene and graphene derivatives (e.g., graphene oxide (GO)) have been incorporated into hydrogels to improve the properties (e.g., mechanical strength) of conventional hydrogels and/or develop new functions (e.g., electrical conductivity and drug loading/delivery). Unique molecular interactions between graphene derivatives and various small or macromolecules enable the fabrication of various functional hydrogels appropriate for different biomedical applications. In this mini-review, we highlight the recent progress in GO-incorporated hydrogels for biomedical applications while focusing on their specific uses as mechanically strong materials, electrically conductive scaffolds/electrodes, and high-performance drug delivery vehicles.

What is Graphene Oxide? What is it used for?



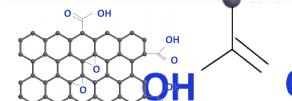
Graphene oxide films are used in the following applications:

- Graphene research.
- Biomedical.
- Solar cells.
- Graphene/polymer composite materials.
- Batteries.
- Supercapacitors.
- Support for metallic catalysts.
- Low permeability materials.



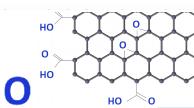
areas include sensing, energy orage, and catal s. The mechan, thermal, electrical, and on g ca projecties render gra hene-based nanc omposites of me allic nanoparticles us f for several bid nedical applications. Epithelial ovar an carcinoma is the fifth most deadly cancer in women; tumors initial espond to chamberapy, but a tually a quire chemorehe developmen novel moles for cancer therapy is essential. This tudy was designed to develop a sir ple, non-toxic, et /ironmentally friendly method or the sonthesis of reduce graphe es xide-silver (rGO-Ag) anoparticle nanocomposites using Tili nurensis plant racts as reducine and stabilizing ants. The anticancer properties of

ОН



Konkuk University, Seoul, Re-

of Korea



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